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Ambient Water Quality Criteria: Chloroform

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CHLOROFORM

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
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CRITERION DOCUMENT

CHLOROFORM

CRITERIA

Aquatic Life

For chloroform, the criterion to protect freshwater aquatic life, as derived using the Guidelines, is 500 µg/l as a 24-hour average and the concentration should never exceed 1,200 µg/l at any time.

For chloroform, the criterion to protect saltwater aquatic life, as derived using procedures other than the Guidelines, is 620 µg/l as a 24-hour average and the concentration should never exceed 1,400 µg/l at any time.

Human Health

For the maximum protection of human health from the potential carcinogenic effects of exposure to chloroform through ingestion of water and contaminated aquatic organisms, the ambient water concentration is zero. Concentrations of chloroform estimated to result in additional lifetime cancer risks ranging from no additional risk to an additional risk of 1 in 100,000 are presented in the Criterion Formulation section of this document. The Agency is considering setting criteria at an interim target risk level in the range of 10^{-5}, 10^{-6}, or 10^{-7} with corresponding criteria of 2.1 µg/l, 0.21 µg/l, and 0.021 µg/l, respectively.

BIBLIOGRAPHIC INFORMATION

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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for chloroform. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has n, ...

KEYWORDS: *Water quality, *Toxicology, *Chloroform, *Water pollution effects(Humans), *Water pollution effects(Animals), *Toxic substances.

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Introduction

Chloroform ($CHCl_3$) was first employed as an anesthetic agent in 1847. Only a small amount was necessary to induce narcosis and its action was more complete than ether (Simpson, 1847). The first reported case of death as a result of chloroform anesthesia-induced liver damage occurred in 1894 (Guthrie, 1894). Chloroform has become obsolete as a widely used anesthetic in favor of other agents with more desirable properties; its uses today are mainly as a chemical solvent and as an intermediate in the production of refrigerants, plastics, and pharmaceuticals (U.S. EPA, 1975). Current annual production of chloroform approaches 120,000 metric tons (U.S. EPA, 1978).

Chloroform ($CHCl_3$; molecular weight 119.39) at ordinary temperatures and pressures is a clear, colorless, volatile liquid with a pleasant, etheric, non-irritating odor and sweet taste (Hardie, 1964; Windholz, 1976). It has a boiling point range of 61 to 62 degrees C, a melting point of -63.5 degrees C, and is non-flammable. There is no flash point (Hardie, 1964; Windholz, 1976). Chloroform is slightly soluble in water (7.42×10^6 µg/l of water at 25 degrees C). It is miscible with alcohol, benzene, ether, petroleum ether, carbon tetrachloride, carbon disulfide, and oils (Windholz, 1976). Chloroform is highly refractive and has a vapor pressure of 200 mm Hg at 25 degrees C (Irish, 1962; Windholz, 1976). Due to its volatile nature, chloroform

has the potential for evaporation to the air from pollution sources or from the water column.

At ambient environmental temperatures, chloroform is thermostable and resists decomposition (Hardie, 1964). However, slow decomposition is observed following prolonged exposure to sunlight in the presence or absence of air, and in the dark when air is present (Hardie, 1964). Chloroform has the potential to react with, and thereby deplete, the ozone layer since studies have shown that phosgene is a decomposiition product of ozone and chloroform (Hardie, 1964). There is no appreciable decomposition of chloroform at ambient temperatures in water even in the presence of sunlight (Hardie, 1964). Aqueous degradation of chloroform is accelerated in the presence of aerated waters and metals such as iron with hydrogen peroxide representing the degradation product (Hardie, 1964).

Chloroform appears to be ubiquitous in the environment in trace amounts and discharges into the environment result largely from chlorination of water and wastewater (U.S. EPA, 1975). Major transport routes are both waterborne and atmospheric.

In controlled laboratory tests, chloroform has been shown to be toxic to aquatic organisms. In mammalian species, chloroform has been demonstrated to be carcinogenic (Eschenbrenner and Miller, 1945) and exhibits both temporary and lasting toxic effects.

Human exposure may be incidental or occupational, or deliberate because of the pre-narcosis euphoria associated with the inhalation of chloroform (Storms, 1973). Humans

are exposed to chloroform by routes other than water ingestion, including food ingestion, inhalation, and skin contact.

Long range exposures have caused both physical and neurological disorders in humans, with liver and kidney toxic responses representing the most prevalent physical pathology. Epidemiological studies hint that there may be a relationship between cancer incidence and ingestion of water containing chloroform. The studies are inconclusive, however, and only add to the weight of evidence suggesting that chloroform exposure may be deleterious.

The chemical apparently does not significantly bioconcentrate in aquatic species (U.S. EPA, 1978) or significantly biomagnify along the food chain to higher trophic levels (Pearson and McConnell, 1975; McConnell, et al. 1975) and evidence suggests that it is metabolized in humans by the liver and kidney to carbon dioxide or it is eliminated unchanged as chloroform through the lungs (Taylor, et al. 1974; McConnell, et al. 1975).

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

Chloroform has been most commonly tested under static test conditions with no measurement of the concentrations of chloroform to which the organisms are exposed. Consequently, the acute toxicity data base will probably underestimate the toxicity because test concentrations in static tests are likely to diminish during the progress of the exposure as a result of loss from water to air.

Acute Toxicity

Bentley, et al. (1975) compared the toxicity of chloroform to rainbow trout and to bluegill and found (Table 1) that the trout was more sensitive. All 96-hour LC50 values, using static methods and unmeasured concentrations, were between 43,800 and 115,000 µg/l. The Final Fish Acute Value calculated from these data after adjusting for the test methods and species sensitivity is 11,000 µg/l (Table 1).

A 48-hour static test with Daphnia magna resulted in an LC50 of 28,900 µg/l (Table 2). After adjustment for static test conditions and use of unmeasured exposure concentrations, the adjusted 48-hour LC50 is 24,478 µg/l. The adjustment to cover 95 percent of all species results in a Final Invertebrate Acute Value of 1,200 µg/l and since this is lower than the Final Fish Acute Value, it is used as the Final Acute Value for freshwater aquatic life.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] and the Methodology Document in order to better understand the following discussion and recommendation. The following tables contain the appropriate data found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

Chronic Toxicity

The chronic effects of chloroform on Daphnia magna were determined (U.S. EPA, 1978), using flow-through methods with measured concentrations. The threshold concentration was between 1,800 and 3,600 (Table 3) or about one-tenth of the static 48-hour LC50. To provide a point estimate of the chronic level, the geometric mean of the range is calculated and the resultant concentration of 2,546 µg/l divided by the adjustment factor for species sensitivity provides an estimate of the threshold concentration for 95 percent of all invertebrates. Since no data are available for fish, the invertebrate value is the only estimate of chronic toxicity and becomes the Final Chronic Value.

Residues

After a 14-day exposure (U.S. EPA, 1978) to radiolabeled chloroform, the bluegill bioconcentrated chloroform by a factor of 6 times (Table 4), and the tissue half-life was less than 1 day. This degree of bioconcentration and short biological half-life suggest that residues of chloroform would not be an environmental hazard to aquatic life.

Miscellaneous

Most of these data are compiled from short exposures of minutes to a few hours in duration (Table 5). With stickleback, goldfish, and orangespotted sunfish, anesthetization or death occurred at concentrations between 97,000 and 494,400 µg/l. None of these data indicate adverse effects at concentrations as low as the data in Tables 1 through 4.

CRITERION FORMULATION

Freshwater - Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 11,000 µg/l

Fish Invertebrate Acute Value = 1,200 µg/l

Final Acute Value = 1,200 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = 500 µg/l

Final Plant Value = not available

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 500 µg/l

0.44 x Final Acute Value = 530 µg/l

The maximum concentration of chloroform is the Final Acute Value of 1,200 µg/l and the 24-hour average concentration is the Final Chronic Value of 500 µg/l. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For chloroform the criterion to protect freshwater aquatic life as derived using the Guidelines is 500 µg/l as a 24-hour average and the concentration should not exceed 1,200 µg/l at any time.

Table 1. Freshwater fish acute values for chloroform (Bentley, et al. 1975)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)
Rainbow trout, *Salmo gairdneri*	S	U	96	66,800	36,500
Rainbow trout, *Salmo gairdneri*	S	U	96	43,800	23,900
Bluegill, *Lepomis macrochirus*	S	U	96	115,000	62,900
Bluegill, *Lepomis macrochirus*	S	U	96	100,000	54,700

* S = static

** U = unmeasured

Geometric mean of adjusted values = 41,600 µg/l $\quad \frac{41,600}{3.9} = 11,000$ µg/l

Table 2. Freshwater invertebrate acute values for chloroform (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)
Cladoceran, Daphnia magna	S	U	48	28,900	24,478

* S = static

** U = unmeasured

Geometric mean of Adjusted values = 24,478 µg/l $\frac{24,478}{21}$ = 1,200 µg/l

Table 3. Freshwater invertebrate chronic values for chloroform (U.S. EPA, 1978)

Organism	Test*	Limits (µg/l)	Chronic Value (µg/l)
Cladoceran, *Daphnia magna*	LC	1,800-3,600	2,546

* LC = life cycle or partial life cycle

Geometric mean of chronic values = 2,546 µg/l $\quad \frac{2,546}{5.1} = 500$ µg/l

Lowest chronic value = 2,546 µg/l

Table 4. Freshwater residues for chloroform (U.S. EPA, 1978)

Organism	Bioconcentration Factor	Time (days)
Bluegill, *Lepomis macrochirus*	6	14

Table 5. Other freshwater data for chloroform

Organism	Test Duration	Effect	Result (µg/l)	Reference
Orangespotted sunfish, Lepomis humilis	1 hr	death	106,890-152,700	Clayberg, 1917
Goldfish, Carassius auratus	30-60 min	50% anesthetized	97,000-167,000	Cherkin & Catchpool, 1964
Threespine stickleback, Gasterosteus aculeatus	20 min	death	296,640-494,400*	Jones, 1947a
Threespine stickleback, Gasterosteus aculeatus	90 min	anesthesia with recovery	207,648*	Jones, 1947a
Ninespine stickleback, Pungitius pungitius	--	avoidance	148,320-296,640*	Jones, 1947b

* Corrected from vol/vol to µg/l

SALTWATER ORGANISMS

Introduction

Only one appropriate test has been reported on the toxicity of chloroform to saltwater aquatic life. Bentley, et al. (1975) conducted a static test with pink shrimp and determined a 96-hour LC50 of 81,500 µg/l. This datum, corrected for test conditions and species sensitivity, results in a Final Invertebrate Acute Value of 1,400 µg/l (Table 6). No other data for effects on saltwater organisms were found.

CRITERION FORMULATION

Saltwater - Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = not available

Final Invertebrate Acute Value = 1,400 µg/l

Final Acute Value = 1,400 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = not available

Residue Limited Toxicant Concentration = not available

Final Chronic Value = not available

0.44 x Final Acute Value = 620 µg/l

No saltwater criterion can be derived for chloroform using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available.

Results obtained for chloroform with freshwater organisms and for structurally similar compounds with both freshwater and saltwater organisms provide an alternate method to estimate a criterion.

With freshwater organisms the Final Chronic Value derived from data for *Daphnia magna* for chloroform is about the same as 0.44 times the Final Acute Value; and with saltwater organisms the Final Chronic Value for structurally similar bromoform is greater than 0.44 times the Final Acute Value.

Therefore, 0.44 times the Final Acute Value is the best estimate of the 24-hour average concentration.

In regard to acute toxicity, freshwater fish are less sensitive than invertebrates species based upon the Final Fish and Final Invertebrate Acute Values. The same is true for two other halomethanes - bromoform and methylene chloride. For freshwater organisms and carbon tetrachloride, a similar relationship exists. Therefore, the absence of acute data for fish is not constraining and the Final Invertebrate Acute value of 1,400 µg/l is used as an estimate for the Final Acute Value. Furthermore, 0.44 times the Final Acute Value is 620 µg/l, which becomes an estimate of the criterion for the 24-hour average concentration.

CRITERION: For chloroform the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 620 µg/l as a 24-hour average and the concentration should not exceed 1,400 µg/l at any time.

Table 6. Marine invertebrate acute values for chloroform (Bentley, et al. 1975)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)
Pink shrimp, *Penaeus duorarum*	S	U	96	81,500	69,030

* S = static

** U = unmeasured

Geometric mean of adjusted acute values = 69,030 µg/l $\frac{69,030}{49}$ = 1,400 µg/l

CHLOROFORM

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Mammalian Toxicology and Human Health Effects

Exposure

Ingestion in Water. In an 80 city study, chloroform was found in all finished drinking water supplies produced from raw water which had been chlorinated (Symons, et al. 1975). Chloroform was usually found in the highest concentration among the four trihalomethanes usually detected. In these finished drinking water supplies, the levels of chloroform, bromodichloromethane, dibromochloromethane, and bromoform ranged from less than 0.1 µg/l to 311 µg/l, not detected to 116 µg/l, not detected to 100 µg/l, and not detected to 92 µg/l, respectively. The highest concentrations of total trihalomethanes were found for those finished drinking water supplies in which surface water was used as a raw source, chlorination on the source water was practiced, and the free chlorine residual from this chlorination was greater than 0.4 mg/l. Total trihalomethane concentrations were generally related to the organic content of the raw water when sufficient chlorine was added to create a chlorine residual. Analysis of the raw source waters showed only minor contributions to the chloroform levels of the finisbed drinking waters inferring the production of chloroform in the chlorination process.

In its Statement of Basis and Purpose for an Amendment to the National Interim Primary Drinking Water Regulations for Trihalomethanes, 1978, the U.S. EPA (1978b) reviewed the latest data on chloroform exposure from drinking water. Using data from NOMS (Natl. Organics Monitoring Study, 1977), an average per capita consumption figure of 2 liters per day, and 100 percent body absorption of chloroform, a total chloroform uptake from water was estimated to be a mean value of 61 mg/year and a maximum value of 343 mg/year. The corresponding NOMS mean and maximum chloroform concentrations for drinking water were 0.083 mg/l and 0.47 mg/l.

Additional evidence of chloroform production as a result of chlorination practices in water renovation was provided by Bellar, et al. (1974). Chloroform concentrations in the influent

and effluent of the Cincinnati, Ohio sewage treatment plant where chlorination was practiced were 9.3 µg/l and 12.1 µg/l, respectively.

Much higher levels of chloroform have been found in wastewater effluents and as the result of accidental industrial spills. Wastewater effluents from rubber and chemical companies in the Louisville, Kentucky area have had chloroform levels as high as 22,000 µg/l (Nat. Acad. Sci., 1978). An accidental spill into the Mississippi River was studied in detail by Neely, et al. (1976) involving the rupturing of two barge tanks and the release of 1.75 million pounds of chloroform. Numerous spills have been detected in the upper Ohio River (Brass and Thomas, 1978) and levels of 50 µg/l persisted for 5 days in March, 1978. Both of these rivers serve as raw water sources for finished drinking water supplies and it is obvious that these incidences contributed abnormally high levels of chloroform to the human population.

Ingestion in Food. McConnell, et al. (1975) reviewed the incidence, significance, and movement of chlorinated hydrocarbons in the food chain. They concluded that chloroform is widely distributed in the environment and is present in fish, water birds, marine mammals, and various foods.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1973) found that the per capita consumption is 18.7 g/day. From the data on the nineteen major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

A measured steady-state bioconcentration factor of six was obtained for chloroform using bluegills containing about 1 percent lipids (U.S. EPA, 1978a). An adjustment factor of 2.3/1.0 = 2.3 can be used to adjust the measured BCF from the 1.0 percent lipids of the bluegill to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for chloroform and the edible portion of all aquatic organisms consumed by Americans is calculated to be 6 x 2.3 = 14.

In food, the typical range of chloroform was found to be 1 to 30 µg/kg. The highest concentration noted was in Cheshire cheese, at 33 µg/kg. It was concluded that chloroform levels in food would not be acutely toxic to humans. Pearson and McConnell (1975) also reviewed the incidence of chlorinated hydrocarbons in various marine organisms and water birds and found that the concentrations of chloroform in edible fish and marine organisms ranged from 3 to 180 µg/kg.

Potrepka (1976) estimated that the consumption of products such as bread derived from chloroform treated (as a fumigant) grains would contribute 0.56 µg of chloroform per day to the adult human diet. This number was derived from the assumption of: 1) consumption of 140 g of bread per day; 2) a chloroform level of 0.4 µg/g in the bread where chloroform was used as the grain fumigant; and 3) chloroform comprises only 1 percent of total fumigant use in the United States.

An exposure level for chloroform in the human diet due to ingestion of beef reared on chloroform fumigated grain can also be calculated. It is assumed that a beef cow consumes an average of 9.07 kg of grain products per day for approximately 150 days of its grow-out period in feed lots. Assuming a typical chloroform level in the grain of 0.06 mg/kg, the total amount of chloroform ingested by the beef cow during its grow-out period is (150) (9.07) (0.06) = 81.6 mg. Fifty percent retention of this total amount of chloroform ingested would set the total body burden in the beef cow at 40.8 mg of chloroform. Assuming a uniform tissue distribution in 450 kg of edible meat in the beef cow, a calculated level of chloroform in the edible meat would be 0.09 mg/kg. A typical adult male who consumes 0.35 kg of meat per day would, therefore, ingest (0.09) x (0.35) = 32 µg of chloroform per day by this dietary source.

Inhalation. The National Academy of Sciences (1978) provided data on the occurrence of six halomethanes in the air. The general background tropospheric concentration of chloroform ranged from 9.8×10^{-5} to 19.6×10^{-5} mg/m^3 with higher concentrations in marine air; lower levels were normally found in continental air samples. Over urban areas, there can be higher concentrations of carbon tetrachloride, chloroform, and methylene chloride. Bayonne, N.J. had the highest measured ambient air concentration of chloroform at 0.073 mg/m^3. Automobile exhausts have been implicated in high urban area chloroform concentrations. Typically, automobile exhausts have chloroform levels of 0.027 mg/m^3. The concentration of chloroform in indoor air rarely exceeds 4.9×10^{-4} mg/m^3.

Dermal. At one time, chloroform as an anesthetic was administered by absorption through the skin. The American Conference of Government Industrial Hygienists (ACGIH, 1977) has stated the potential danger of chloroform poisoning by this route. Today, dermal exposure is rare and is applicable to that small segment of the population engaged in the manufacture and use of chloroform and its products.

Pharmacokinetics

Absorption. Chloroform can be absorbed by the mammalian body by three routes of administration: 1) chloroform vapors can be inhaled and absorbed by the lungs; 2) chloroform can be ingested and absorbed from the gastrointestinal tract; and 3) it can be absorbed through skin. With airborne exposure the chloroform level in the blood initially rises rapidly, and then more slowly, until an equilibrium between blood concentration and inhaled air concentration is reached. This equilibrium requires 80 to 100 minutes following initial exposure. The efficiency of chloroform absorption by this route is 49 to 77 percent (Lehmann and Hasegawa, 1910). Studies on the oral administration of chloroform show absorption efficiency from the gastrointestinal tract to be approximately 100 percent (Fry, et al. 1972). At one time chloroform was used as an anesthetic via dermal administration and subsequent absorption through the skin.

Distribution. Once absorbed, chloroform is found in all mammalian body organs at concentrations which vary with the depth

and duration of the exposure. The highest concentration has been noted in the peripheral nerves. Additionally, chloroform is transported across the placenta and concentration in the liver of the fetus can be higher than in the corresponding maternal organ.

Yesell, et al. (1976) reports strain differences for chloroform content in mice. Kidney homogenates in one strain contained twice as much labeled chloroform as another strain. Kidneys of male mice are known to accumulate more chloroform than do those of females although the converse is true in the case of the liver.

Metabolism. In mammals only a small fraction of absorbed chloroform is metabolized to CO2 and chloride, the latter being excreted in the urine. In mammalian tissue, evidence indicates that chloroform is metabolized by both the liver and the kidney (Taylor, et al. 1974). Chloroform is converted to carbon dioxide and excreted by the lung (Fry, et al. 1972), but it remains primarily as chloroform and is excreted in urine, feces, and in expired air through the lungs (McConnell, et al. 1975; Fry, et al. 1972).

In the rat, intraduodenal doses of 1,483 mg of radioactively labeled chloroform per kg body weight gave no evidence of other chloromethanes being formed (von Oettingen, 1964). Eighteen hours after dosing, 74 percent of the radioactivity from chloroform had appeared in the exhaled air as chloroform and 3.6 percent as carbon dioxide.

In experiments with mice it has been shown that binding of radioactivity occurs strongly in the areas of the liver and kidney that are made necrotic by chloroform, and that the tissue binding and necrosis are enhanced when the animal is pretreated with phenobarbital and other agents known to induce liver microsomal enzyme systems. Similarly, the tissue binding and necrosis are diminished when the animals are pretreated with known inhibitors of this enzyme system (Ilett, et al. 1973). The implication is that some metabolite of the administered chloroform, generated by the liver enzyme system, is binding covalently to the tissue, causing the tissue damage. The results are essentially the same when two biochemical correlates of liver toxicity are measured instead of tissue necrosis (Lavigne and Marchand, 1974).

Excretion. Fry, et al. (1972) studied a group of adult humans that ingested capsules containing 500 mg of 13C labelled chloroform. Greater than 96 percent of the administered radioactivity was exhaled within 8 hours. Unchanged chloroform was excreted by this route with an efficiency of 18 to 67 percent. Less than 1 percent of the radioactivity appeared in the urine. Those people with a higher tissue fat content exhaled less unchanged chloroform in the 8-hour period and presumably more CO2. A kinetic analysis of Fry's data on two people by Chiou (1975) showed that, extrapolated to infinite time, the fraction metabolized to CO2 is 46 percent for a male and 58 percent for a female, and the rest is exhaled as chloroform. The

half-life of chloroform in the blood and in expired air is approximately 1.5 hours.

Effects

Toxicity. Human exposure to chloroform may be accidental or intentional via inhalation, ingestion, injection, or by cutaneous contact (Gonzales, et al. 1954; Schroeder, 1965). The first reported case of death as a result of chloroform anesthesia-induced liver damage occurred in 1894 (Guthrie, 1894). Toxic effects include local irritation (hyperemia, erythemia, moisture loss) at the site of entry via skin absorption (Malten, et al. 1968), central nervous system depression, gastrointestinal irritation (Challen, et al. 1958), hepatic and renal damage, and possible cardiac sensitization to adrenalin (Fuhner, 1923; Althausen and Thoenes, 1932; Cullen, et al. 1940).

Chloroform is considered to be moderately toxic on an acute basis. It is several times more potent than carbon tetrachloride as a depressant of the central nervous system when inhaled, but clinical experience suggests that it is less toxic than carbon tetrachloride when taken orally. The ingestion of 263 grams has been survived, although ingestion of much smaller amounts has produced serious illness. The mean lethal dose is approximately 44 grams (Gosselin, et al. 1976).

Studies or cases of habitual chloroform usage in humans over a period of not less than 1 nor greater than 15 years, with daily

exposure ranging from 20 drops to 100 g, have rendered observation of neurological distress, occasional lethargy, despondency, rapid alterations of temperament, nausea, vomiting, tumors, ataxia, and delerium. Post mortem examination of a chloroform poisoning victim showed moderate degenerative cerebellar changes, slightly thickened meninges, and dilation of blood vessels (Browning, 1885; Friedlander, 1885; Schonfeld, 1932; Heilbrunn, et al. 1945).

The NIOSH Criteria Document (1974) contains a tabulation of the effects of chronic chloroform exposure on humans. One 33-year-old male who habitually had inhaled chloroform for 12 years was noted to have the psychiatric and neurologic symptoms of depression, loss of appetite, hallucination, ataxia, and dysarthria. Other symptoms from habitual use are moodiness, mental and physical sluggishness, nausea, rheumatic pain, and delirium.

Most human toxicological data have resulted from the use of chloroform as a general anesthetic in operations. Delayed chloroform poisoning has often occurred in obstetrical cases after delivery. The delayed toxic effects were usually preceeded by a latent period of from a few hours to one day. Initially drowsiness, restlessness, jaundice, and vomiting occurred. Then fever, elevated pulse rate, liver enlargement, abdominal tenderness, delirium, coma, and abnormal findings in liver and kidney function tests followed. Death often ensued, usually 3 to 10 days post partum. Autopsy reports generally described the

liver as having a bright yellowish color, and on microscopy, fatty infiltration with necrosis was found. Other hepatotoxic effects have been reviewed (NIOSH, 1974). Numerous animal studies have shown that chloroform causes fatty infiltration and necrosis of the liver. None of these studies involved long-term exposures to low concentrations. However, these studies show that hepatotoxic effects of chloroform can occur as the results of ingestion, inhalation, or intravenous administration (NIOSH, 1974). Although the causes of death in most cases of chloroform poisoning have been attributed to necrosis of the liver, there has also been evidence at autopsy of renal damage, including albumin and red blood cells in urine, elevated blood urea, an 18 percent decrease in prothrombin after surgery, and fatty degeneration. Cardiac irregularities were found frequently in 1936 during electrocardiographic (ECG) surveillance of surgical procedures.

A case of pulmonary toxicity secondary to an intentional intravenous injection of chloroform has been reported (Timms and Moser, 1975). Chloroform poisoning has resulted in symptoms similar to those of marked hemolytic anemia. Chloroform has induced hemolysis of human erythrocytes *in vitro* (Belfiore and Zimmerman, 1970).

Malten, et al. (1968) reported that chloroform exposure ultimately results in an injury to only the horny layer of skin in humans, and that the skin often responds with the formation of a temporary protective barrier.

There have been few studies of industrial worker exposure. Challen, et al. (1958) reported on a study of workers in a confectionery firm in England that manufactured medicinal lozenges. In 1950, the workers began to complain of chloroform vapors given off during the production of the lozenges. These workers were placed on a reduced work week to alleviate their complaints of lassitude, flatulence, water brash (British term indicative of symptoms of dyspepsia), dry mouth, thirst, depression, irritability, and frequent and "scalding" micturition, but this action was not successful, and finally the workers refused to work on that particular process. In 1954, a new team of operators was engaged and in 1955 a system of exhaust ventilation was installed, after which manufacturing proceeded without interruption.

Clinical investigations of three different groups of workers in this manufacturing plant were performed by Challen, et al. (1958). One group of eight employees was termed the "long service operators." These were people who refused to continue in the lozenge department after they experienced the previously described symptoms. This group of workers, when exposed to chloroform vapor in concentrations ranging from 376 to 1,158 mg/m^3, had been observed staggering about the work area. After terminating work in the lozenge department the "long service operators" reported experiencing nausea and stomach upset after even short exposures to chloroform.

A second group of nine employees termed the "short service operators," were the replacements of the "long service operators." Two of these nine employees did not report unpleasant experiences from chloroform exposure. Among the other seven, five reported dryness of the mouth and throat at work; two were subject to lassitude in the evening; one complained of lassitude and flatulence at work; and the experiences of two others were similar to those of the "long service operators." The "short service operators" worked in locations where the chloroform concentrations ranged from 112 to 347 mg/m^3.

A third group of five employees who worked in other departments of the firm served as controls and exhibited no symptoms. Neither tests of liver function (thymol turbidity, thymol flocculation, direct van den Bergh, and serum bilirubin), clinical examinations, nor urinary urobilinogen showed significant differences among the three groups of workers.

Bomski, et al. (1967) reported on liver injury from chloroform exposure among workers in a pharmaceutical factory in Poland. The study included the entire group of 295 workers who were exposed to chloroform in the course of production. Of these, 68 were exposed to chloroform for 1 to 4 years and still were in contact with chloroform, 39 had chloroform contact at one time, but were no longer exposed, 23 had viral hepatitis with icterus 2 to 3 years earlier and were designated as posticterus controls and were working in a germ-free area, and 165 worked in a germ- free area with no history of viral hepatitis. Blood

pressure, blood morphology, uribakysis, blood albumin, serum protein, thymol turbidity, zinc sulfate turbidity, the "Takata-Ara" sulfate (colorimetric) test, urobilinogen, SGOT, and SGPT were measured in all. A complete medical history was taken. Sixty of the people were hospitalized for determination of BSP clearance and urinary urobilinogen.

The air in the production room was sampled and chloroform concentrations were determined using the Grabowicz method. The concentration of chloroform ranged from 9.8 to 1,002 mg/m^3. No other concentration measurements were reported nor was there any mention of the frequency of sampling.

The authors compared the frequency of viral hepatitis and jaundice among a group of inhabitants of the city, 18 years and older, with that of the same 68 pharmaceutical workers who were exposed to chloroform. The results showed that in 1960, 0.35 percent of city inhabitants had viral hepatitis, while 16.67 percent of the chloroform exposed workers had viral hepatitis. In 1961, the frequency of viral hepatitis for city inhabitants was 0.22 percent and the frequency among the chloroform workers was 7.50 percent. In 1962 the frequency of viral hepatitis was 0.38 percent for city inhabitants and 4.4 percent for workers exposed to chloroform. The authors suspected that the toxic liver changes occurring as a result of exposure to chloroform promoted a viral infection is such cases, but they did not give information on the incidence of viral hepatitis among the other

groups of plant workers, which might have helped resolve questions about sanitary practices and facilities in the plant.

The majority of the workers who were in contact with chloroform during the investigation period covered in this study complained of headache, nausea, belching, and loss of appetite. Among the 68 workers using chloroform, 19 cases of splenomegaly were found, compared to none in the controls.

The frequency of enlarged livers (17 out of 68) among workers exposed to chloroform exceeded the frequency of enlarged livers in two of the other groups (5 out of 39, and 2 out of 23). Livers were judged to be enlarged if they extended at least 1 cm beyond the rib arch in the midclavicular line. The upper margin was apparently not measured. In three of the 17 chloroform workers with enlargement of the liver, toxic hepatitis was diagnosed on the basis of elevated serum enzyme activities and elevated serum gamma globulin, but the measured amounts of these serum constituents in these three workers were not reported. In the remaining 14 cases of liver enlargement, fatty liver was diagnosed.

Intraperitoneally injected chloroform can be nephrotoxic in mice (Klaassen and Plaa, 1967a). The acute LD50 value for male mice was 1,800 mg/kg body weight; for females, 1,900 mg/kg body weight. Male mice demonstrated renal dysfunction at 116 mg/kg body weight, but females did not exhibit renal dysfunction at any

time during or after exposure to even a lethal dose of chloroform.

Intragastric administration of 250 mg of chloroform/kg body weight to rats showed gross pathological changes to both renal and hepatic tissues (Torkelson, et al. 1976). The intragastric LD50 for chloroform was 2,000 mg/kg body weight with most deaths occurring in 2 to 4 hours.

Rats, guinea pigs, and rabbits received repeated inhalatory exposure to chloroform at 85 ppm, 50 ppm and 25 ppm (415, 244, and 122 mg/m^3 respectively) for 7 hours per day, 5 days per week for up to 203 days. Dogs were similarly exposed only to a chloroform concentration of 122 mg/m^3. The results of these studies are reported in Table 7.

The effects of chlororform on kidney and liver function in mongrel dogs have been reported (Klaassen and Plaa, 1967b). Male and female dogs received intraperitoneal injections of chloroform in corn oil. The 24-hr. LD50 was estimated to be 1,483 mg/kg body weight using the "up and down" method of Brownlee, et al. (1953).

Table 7. -Effects of chloroform innalation on four laboratory animal species (Torkelson, et al. 1976)

Organism (Sex)	Concentration (mg/m³)	Effects
Rats: male	415	pneumonia, renal symptoms, hepatic degradation
Female	415	renal & hepatic patnology
Guinea Pigs: male	415	no effects
female	415	pneumonitis
Rabbits: male	415	pneumonitis, hepatic necrosis
female	415	hepatic, renal pathology
Rats: male	244	symptoms less severe than reported at 415 mg/m³
female	244	less affected than males
Guinea Pigs: male	244	normal
female	244	normal
Rabbits: male	244	normal
female	244	normal
Dogs: male	122	normal
female	122	microscopic changes in kidney

In male rats, chloroform has been demonstrated to be hepatotoxic. Experiments have elucidated the role of microsomal amidopyrine N-demethylase activity in the hepatotoxic response (Gopinath and Ford, 1975). Pretreatment with phenobarbitone sodium or phenylbutazone will induce this enzyme and potentiate the hepatotoxic effects of chloroform, i.e., necrotized cells, up to 1,000 percent over control values. On histological examination, degenerative cells were also apparent. Pretreatment with sodium diethyl-dithiocarbamate and carbon disulfide has been shown to protect against liver damage, with no necrotized regions apparent histologically. Pretreatments lasted from 1 hour to 14 days prior to a single oral dose of chloroform.

Toxic effects due to a dermal route of administration have been demonstrated both in non-human mammals and humans. Torkelson, et al. (1976) reported on adverse effects in the rabbit. One to two 24-hour applications, on a cotton pad bandaged on the shaven belly of rabbits, produced a slight hyperemia with moderate necrosis and a resulting eschar formation. Healing appeared to be delayed on the site as well as on abraded areas treated in the same way. Single applications of as low as 1,000 mg per kilogram of body weight for 24 hours under an impermeable plastic cuff resulted in degenerative changes in the kidney tubules. Chloroform dropped into the eyes of rabbits produced slight injury which required one week to heal.

Synergism and/or Antagonism. Pretreatment with alcohols, barbiturates, and other chemicals such as DDT increased the toxic effects of chloroform, apparently by lowering the threshold for its necrotic action. Studies by Ilett, et al. (1973) indicate that this synergistic effect may be related to enhanced tissue binding.

Kutob and Plaa (1961) found that ethanol pretreatment of mice increased the toxic effects of chloroform on the liver. McLean (1970) demonstrated the potentiating effects of other agents. Phenobarbital and DDT increased the liver hydroxylating enzyme activity and the toxicity of chloroform was more than doubled by the pretreatment with these chemicals as measured by the LD50.

Animals on high fat or protein-poor diets are more susceptible to hepatotoxicity from chloroform whereas diets high in carbohydrates and proteins have a protective effect (von Oettingen, 1964).

Teratogenicity. In 1974, Schwetz, et al. demonstrated the effects of repeated exposures to chloroform on rat embryos and fetal development. Pregnant Sprague-Dawley rats were exposed to airborne chloroform at 147, 489, and 1466 mg/m^3 for 7 hours/day on days 6 to 15 of gestation. Pregnant rats exposed to 489 mg/m^3 showed a significant increased incidence of fetal abnormalities compared to controls. There were significantly increased incidences of acaudia (taillessness), imperforate anus, subcutaneous edema, missing ribs, and delayed sternebrae ossification. Rats exposed to 147 mg/m^3 showed significant

increased incidences of delayed skull ossification and wavy ribs, but exhibited no other deleterious effects compared to controls.

Thompson, et al. (1974) reports in a range-finding study in rats, that oral doses of chloroform of 126 mg/kg/day and greater produced dose-related maternal toxicity. Doses of 316 mg/kg/day and greater caused acute toxic nephrosis and hepatitis and death of dams, as well as fetotoxicity. Results of a range-finding study in the rabbit suggest this species to be more sensitive to the effects of chloroform, in that oral doses of 100 mg/kg/day or higher were toxic to both the dam and fetus.

In these teratology studies, the occurrence of adverse clinical effects in the females of both species, and of hepatotoxicity in the rabbit indicates that maximum tolerated doses of chloroform were used. Even at maternal toxic levels, only mild fetal toxicity in the form of reduced birth weights was observed. Dose levels as high as 126 mg/kg/day in the rat and 50 mg/kg/day in the rabbit were neither embryocidal nor teratogenic.

The finding of fetal anomalies by Schwetz, et al. (1974) following exposure of pregnant rats to chloroform by inhalation and their absence in the Thompson studies following oral exposure, may be attributed to the difference in routes of administration. Blood concentrations and tissue distribution of chloroform in maternal and fetal compartments would undoubtedly be affected by the route and duration of maternal exposure which differed in the two studies, i.e., continuous exposure 7 hours

daily in the inhalation study compared to one or two short periods of exposure per day in the oral study.

The increased incidence of spontaneous abortion in exposed female workers and of congenital abnormalities among their children, and the same increases among wives and children of exposed men prompted establishing criteria for halogenated anesthetic gases and vapors (NIOSH, 1977).

Mutagenicity. Chloroform has been tested by the histidine-revertant mutation system employing Salmonella typhimurium tester strains and found to be negative. Interestingly, the other trihalomethanes formed by chlorination of drinking water were positive in such tests (Simmon, et al. 1977).

Carcinogenicity. Eschenbrenner and Miller (1945) studied the effect of repeated oral doses of chloroform on the induction of hepatomas in mice. A graded series of necrotizing and nonnecrotizing doses of chloroform was administered. Three-month-old strain A mice which had an incidence of spontaneous hepatomas of less than 1 percent at 16 months were given intragastric doses of olive oil solutions at 5 ml/kg body weight. The chloroform content of the solutions varied so that the chloroform doses were respectively 1.6, 0.8, 0.4, 0.2, or 0.1 ml/kg (2373, 1187, 593, 297, 148 mg/kg).

The presence or absence of liver necrosis was determined by microscopic examination of liver sections taken 24 hours after administration of a single dose of chloroform. The livers of animals receiving doses of 297 and 148 mg/kg of chloroform showed no necrosis. However, with these doses, necrotic areas were observed in the kidneys of males, but not of females. This sex difference of renal necrotic lesions was observed at all concentrations. No sex difference was observed for liver necrosis. Twenty-four hours after a single dose of 593 mg/kg or more of chloroform, there was extensive necrosis of liver cells around the central veins. Thirty doses were given at 4-day intervals to test for any carcinogenic effect. (This was the schedule under which a hepatoma incidence of 100 percent was obtained when carbon tetrachloride was used.) Hepatomas were found only in animals that received necrotizing doses of chloroform (at least 593 mg/kg) and which were killed 1 month after the last dose. These were seen only in female mice, which could reflect the lower tolerance to chloroform for males, i. e., the males might have died earlier of renal necrosis, before onset of malignant changes. The authors inferred that necrosis was a prerequisite to tumor induction.

In 1976 the National Cancer Institute released its Report on Carcinogenesis Bioassay of Chloroform. This study followed the protocol that had been developed for testing a series of chemicals by the Carcinogenesis Bioassay Program of the Division of Cancer Cause and Prevention. The work was carried out under contract with the Hazleton Laboratories of America, Inc.

A carcinogenesis bioassay of USP grade chloroform was conducted using male Osborne-Mendel rats and both male and female B6C3F1 mice. Chloroform was administered orally (by gavage) in corn oil to 50 animals of each sex and at two dose levels five times per week for 78 weeks. Rats were started on the test at 52 days of age and killed after 111 weeks. The dose levels for males were 90 and 180 mg/kg body weight. Female rats were started at 125 and 250 mg/kg, reduced to 90 and 180 mg/kg after 22 weeks, with an average level of 100 and 200 mg/kg for the study. A decrease in survival rate and weight gain was evident for all treated groups. The most significant observation (P = .0016) was kidney epithelial tumors in male rats with incidences of: 0 percent in controls, 8 percent in the low dose, and 24 percent in the high dose groups (Table 8). Although an increase in thyroid tumors was also observed in treated female rats, this finding was not considered biologically significant.

Table 8. - Statistically significant tumor incidence in rats (National Cancer Institute, 1976)

	Males			
	Controls		Low Dose	High Dose
	Colony	Matched		
Kidney epithelial tumors/animals	0/99	0/19	90 mg/kg 4/50 (8%)	180 mg/kg 12/50 (24%)
P value	0.0000	0.0016		

Microscopically, the appearance of these epithelial tumors varied from circumscribed, well-differentiated tubular-cell adenomas to highly plecmorphic, poorly differentiated carcinomas which had invaded and metastasized. The cells in adenomas were relatively uniform and polygonal, with abundant eosinophilic cytoplasm. Nuclei were central or basal in location, with minimal atypia and little increase in mitotic index. Most carcinomas were very large and replaced a considerable portion of the renal parenchyma. They were poorly circumscribed and infiltrated surrounding normal tissues. These were or irregular sheets, nests, and tubular arrangements of cells with varying

degrees of anaplasia and increased nuclear/cytoplasmic ratio. The nests of cells were often surrounded by a delicate fibrovascular stroma, and central necrosis was sometimes present in the more anaplastic neoplasms. A papillary glandular pattern was rarely observed.

Mice were started on test at 35 days and killed after 92 to 93 weeks. Initial dose levels were 100 and 200 mg/kg for males and 200 and 400 mg/kg for female mice. These levels were increased after 18 weeks to 150/300 and 250/500 mg/kg, respectively, so that the average levels were 138 and 277 mg/kg for males and 238 and 477 mg/kg for female mice. Survival rates and weight gains were comparable for all groups except high dose females which had a decreased survival. Highly significant increases ($P=.001$) in hepatocellular carcinoma were observed in both sexes of mice with incidences of 98 percent and 95 percent for males and females at the high dose, and 36 and 80 percent for males and females at the low dose (Table 9). This compares with 6 percent in both matched and colony control males and 0 percent in matched control females and 1 percent in colony control females. Nodular hyperplasia of the liver was observed in many low dose male mice that had not developed hepatocellular carcinoma.

Table 9. - Heptoceullular carcincma incidence in mice
(National Cancer Institute, 1976)

	Controls		Low	High
	Colony	Matched	Dose	Dose
Male	5/77 (6%)	1/18 (6%)	138 mg/kg 18/50 (36%)	277 mg/kg 44/45 (98%)
Female	1/80* (1%)	0/20 (0%)	238 mg/kg* 36/45 (80%)	477 mg/kg 39/41 (95%)

*Data used for calculation of cancer risk in Criteria Formulation section of this document.

The incidence of hepatocellular carcinoma is significantly elevated in both sexes of mice. A high incidence of these tumors was observed in all treated groups, and the difference was determined to be statistically significant at the p=0.001 level. These lesions were observed in animals which died as early as 54 weeks following initial exposure. The increase in lesion development observed is due to the occurrence of a specific type of tumor, hepatocellular carcinoma. The hepatocellular carcinomas observed in the various test and control groups comprised the full spectrum of morphology of this entity. The tumors varied from those composed of well-differentiated hepatocytes with a relatively uniform arrangement, to those which

were very anaplastic and poorly differentiated with numerous mitotic figures. Various types of hepatocellular carcinomas described in the literature were seen, including those with an orderly cord-like arrangement of neoplastic cells, those with a pseudoglandular pattern resembling adenocarcinoma, and those composed of sheets of highly anaplastic cells with little tendency to form a cord or gland-like arrangement. The diagnosis of hepatocellular carcinoma was based primarily on histologic characteristics of the neoplasm. Hepatocellular carcinomas were found to have metastasized to the lung in two low dose males and two high dose females, and to the kidney in a high dose male.

A search of the literature has not revealed long term followup studies on industrially exposed populations. It is expected that there would be a long latency period, as that which occurs with the action of other carcinogens. A plant survey of workers who had been exposed for only a few years would not be expected to show a significant increase in cancer.

When data on chloroform concentrations became available from U. S. EPA's surveys of drinking water, a correlation was noted with cancer death rates for all sites in the survey (McCabe, 1975). Fifty cities where at least 70 percent of the population was served by the water sampled had chloroform concentrations

measured in 1975 that could be compared with cancer mortality in 1969-71. A statistically significant correlation was found between the age, sex, and race adjusted death rate for total cancer and chloroform levels.

Epidemiology studies of cancer frequency for trihalomethanes of which chloroform is a primary chemical specie began to appear in 1974. EPA asked a number of research groups to evaluate whether there was a relationship between cancer rates and chloroform and other trihalomethanes (THM) in water supplies. Most of the EPA requested studies used indirect evidence of the presence of THM in water supplies while two others used direct measurements of chloroform and other THM.

This type of study has been extended by Cantor, et al. (1977) who looked at the association between each of 16 cancer rates in whites, by sex and levels of trihalomethanes separated into chloroform and nonchloroform components. Exposure information came from the National Organics Reconnaissance Survey and the U. S. EPA Region V Survey of 1975. Seventy-six counties in which more than 50 percent of the population was served by the sampled and assayed water supply were included in the study. The most consistent finding was an association between bladder cancer mortality rates and trihalomethane levels. The association was observed in both sexes and showed a gradient of increasing degree of correlation when counties were grouped by percent of the county population served by the water supply. The correlations noted were stronger with the brominated trihalomethanes than with chloroform.

Hogan, et al. (1977) used approximately the same data base and applied various statistical procedures to the data in order to determine the appropriateness of the statistical model. The results were similar to previous studies showing positive correlation between rectal-intestinal and bladder cancer mortality rates and chloroform levels in drinking water, when a weighted regression analysis was applied.

Given the number of epidemiology studies appearing, the EPA asked the National Research Council to review the studies. NAS (1978b) provided a review of 10 epidemiology studies including the ones previously mentioned and concluded that the association with cancer and THM was small and that there was a large margin of error. In most of the studies, the THM exposure and duration levels were inferred and confounding factors known to affect cancer incidence were inadequately controlled. The failure of these studies to clearly establish a positive or negative cause and effect relationship between THM's and cancer resides to some extent in the complexities inherent in doing such studies.

CRITERION FORMULATION

Existing Guidelines and Standards

The Ocupational Safety and Health Administration's limit for chloroform in work place air is 50 ppm or 244 mg/m^3. This is a "ceiling value" for a maximum 10-minute exposure that at no time shall be exceeded. NIOSH promulgated a criterion of 10 ppm (48.9 mg/m^3) in 1974. This criterion was applied to a time-weighted exposure for as high as 10 hours per day and a 40-hour work week. Following the National Cancer Institute's (NCI) study of chloroform, NIOSH on June 9, 1976 reduced this allowable time-weighted average exposure criterion to 2 ppm (9.8 mg/m^3).

Based on available health information, a safe level of airborne exposure to halogenated agents could not be defined. Since a safe level of occupational exposure to halogenated anesthetic agents could not be established by either animal or human investigations, NIOSH recommended that airborne exposure be limited to levels no greater than the lowest level detectable using the sampling and analysis techniques recommended (NIOSH, 1977). Although chloroform at the present is not usually used as an anesthetic, it is included in the criteria and is limited to 2 ppm or 9.8 mg/m^3.

If a procedure that converts this air limit to a water limit is employed, the equivalent exposure in water would be 34.9 mg/l (Stokinger and Woodward, 1958). In this method, complete absorption from inhalation and ingestion

is assumed. The inhalation absorption may be closer to 50 percent and the equivalent water exposure would then be 17.4 mg per liter. The occupational limits apply to the healthy working-age population and even then if exposure level is half the limit, comprehensive medical surveillance is required. To use the occupational limit as a guide for the general population, an application factor of 100 can be used. Thus, an equivalent level in water would be 174 µg/l. It must be remembered that the occupational limit for chloroform is based on the lowest level detectable in air using NIOSH's recommended analytical techniques and does not necessarily represent a level adequate to protect man.

In general, the use of inhalation data assumes an 8-hour day, time-weighted average, occupational exposure in the working place with workers inhaling the toxic substance throughout such a period. Exposures for the general population should be considerably less. Such worker-exposure inhalation standards are inappropriate for the general population since they presume an exposure limited to an 8-hour day, an age bracket of the population that excludes the very young and the very old, and a healthy worker prior to exposure. Ingestion data are far superior to inhalation data when the risks associated with the food and water of the aquatic environment are being considered.

Following the NCI study of chloroform, the Food and Drug Administration took action to halt the use of chloroform in drug products, cosmetic products, and food contact

materials (41 FR 15026, 15029 April 9, 1976). The Environmental Protection Agency has issued a notice of "rebuttable presumption" against continued registration of chloroform-containing pesticides (41 FR 14588 April 6, 1976).

The Environmental Protection Agency has also proposed an amendment which would add to the National Interim Primary Drinking Water Regulations a section on the control of organic halogenated chemical contaminants in drinking water (43 FR 5756 Feb. 9, 1978). The proposed limit for total trihalomethanes, which includes chloroform, is 100 µg/l. This limit was set largely on the basis of technological and economic feasibility. Originally the limit will apply only to water supplies serving greater than 75,000 consumers; this is intended to provide an orderly upgrading of drinking water treatment in the country. The basis and purpose of the regulation are discussed in a paper by the Office of Drinking Water issued in January 1978 (U.S. EPA, 1978b). This document contains a number of estimates of cancer risk attributable to the presence of chloroform in drinking water. One of these, performed by the National Academy of Sciences, using a linear non-threshold extrapolation from animal data, estimated that the lifetime risk would fall between 1.5×10^{-7} and 17×10^{-7} per microgram of chloroform per liter of water consumed daily depending upon the data set employed. The upper 95 percent confidence estimates would range between 3×10^{-7} and 22×10^{-7} per microgram per liter per day.

Current Levels of Exposure

The National Academy of Science (NAS, 1978a) assembled data based on human exposure to chloroform. Their calculations of human uptake are based on fluid intake, respiratory volume, and food consumption data for "reference man" as compiled by the International Commission for Radiological Protection. Table 10 from the NAS report is reproduced to show their estimates of chloroform uptake from fluids. Table 11 presents the data on relative human uptake from the three sources.

The uptake of chloroform from the atmosphere at minimum levels of exposure is about 10 times greater than from fluids. At maximum exposure levels, the chloroform uptake from fluids is slightly less than that from the atmosphere. At typical exposure levels, however, the human uptake from fluids is two to three times greater than from the atmosphere, with slight variation by sex and age noted.

In its Statement of Basis and Purpose for an Amendment to the National Interim Primary Drinking Water Regulations on Trihalomethanes, the U.S. EPA (1978b) estimated the total human exposure to chloroform. The estimates have basic assumptions that are roughly comparable but not exactly the same as those used by the NAS (1978a), use newer values for chloroform content in drinking water from NOMS data, and provide estimates for human adults only. See Table 12 for the exposure estimates.

Table 10. - Chloroform uptake from fluids (mg/yr) assuming 100 percent absorption[a] (NAS, 1978a)

		Adult Man			Adult Woman			Child (5-14 Yr)		Child (10 Yr)
Exposure	Fluid	Min. Fluid Intake	Max. Fluid Intake	Refer. Man Intake	Min. Fluid Intake	Max. Fluid Intake	Refer. Man Intake	Min. Fluid Intake	Max. Fluid Intake	Refer. Man Intake
Minimum Concentration Exposure (0.0001 mg/l)	Tap Water	0.016	0.027	0.005	0.016	0.027	0.004	0.020	0.029	0.007
	Other[b]	0.012	0.053	0.055	0.012	0.053	0.040			0.027
	Total Fluid	0.037	0.088	0.071	0.037	0.088	0.051	0.036	0.061	0.051
Median Concentration Exposure (0.021 mg/l)	Tap Water	3.44	5.59	1.15	3.44	5.59	0.77	4.14	6.06	1.53
	Other[b]	2.45	11.1	11.5	2.45	11.1	8.43			5.75
	Total Fluid	7.57	18.4	14.9	7.67	18.4	10.7	7.67	12.8	10.7

	Tap									
Maximum	Water	60.0	97.5	20.1	60.0	97.5	13.4			26.7
Concentration										
Exposure	Other[b]	42.7	194	200	42.7	194	147	72.1	106	100
(0.366 mg/l)	Total									
	Fluid	134	321	261	134	321	187	134	223	187

aCalculated by multiplying the exposure concentration (ug/l)(from Table 6.6)x fluid intake (l/yr)(from Table 6.1 for minimum and maximum intakes and Table 6.2 for reference man intakes), and dividing by 1000 ug/mg = mg/yr.

bIncludes water based drinks, such as tea, coffee, soft drinks, beer, cider, wine.

Table 11 - Relative human uptake of carbon tetrachloride (CCl_4) and chloroform ($CHCl_3$) from environmental sources (mg/year) (NAS, 1978a)

	At Minimum Exposure Levels[a]					
	Adult Man		Adult Woman		Child	
Source	CCl_4	$CHCl_3$	CCl_4	$CHCl_3$	CCl_4	$CHCl_3$
Fluid Intake	0.73	0.037	0.73	0.037	0.73	0.036
Atmosphere	3.60	0.41	3.30	0.37	2.40	0.27
Food Supply	0.21	0.21	0.21	0.21	0.21	0.21
Total	4.54	0.66	4.24	0.62	3.34	0.52

	At Typical Exposure Levels[b]					
	Adult Man		Adult Woman		Child	
Source	CCl_4	$CHCl_3$	CCl_4	$CHCl_3$	CCl_4	$CHCl_3$
Fluid Intake	1.78	14.90	1.28	10.70	1.28	10.70
Atmosphere	4.80	5.20	4.40	4.70	3.20	3.40
Food Supply	1.12	2.17	1.12	2.17	1.12	2.17
Total	7.70	22.27	6.80	17.57	5.60	16.27

Table 11 (continued)

At Maximum Exposure Levels (c)

Source	Adult Man		Adult Woman		Child	
	CC14	CHC13	CC14	CHC13	CC14	CHC13
Fluid Intake	4.05	321	4.05	321	1.83	223
Atmosphere	618	474	567	434	405	310
Food Supply	7.33	16.4	7.33	16.4	7.33	16.4
Total	629	811	578	771	414	549

(a) Minimum conditions of all variables assumed: Minimum exposure-minimum intake for fluids; minimum exposure-minimum absorption for atmosphere; and minimum exposure-minimum intake for food supplies.

(b) Typical conditions of all variables assumed. For CC14: 0.0025 mg/l-reference man intake for fluids; average of typical minimum and maximum absorption for atmosphere; and average exposure and intake for food supplies. For CHC13: median exposure-reference man intake for fluids; average of typical minimum and maximum absorption for atmosphere; and average exposure and intake for food supplies.

(c) Maximum conditions of all variables assumed: maximum exposure intake for fluids; maximum exposure-maximum absorption for atmosphere; and maximum exposure-maximum intake for food supplies.

Table 12. Uptake of Chloroform for the Adult Human from Air, Water, and Food (U.S. EPA, 1978b)

Source	Adult mg/yr	Percent uptake
Maximum Conditions		
Atmosphere	204	36
Water	343	61
Food Supply	16	3
Total	563	100.00
Minimum Conditions		
Atmosphere	0.41	13
Water	0.73	23
Food Supply	2.00	64
Total	3.14	100.00
Mean Conditions		
Atmosphere	20.0	22
Water	64.0	69
Food Supply	9.00	10
Total	93	100.00

U.S. EPA, Statement of Basis and Purpose for an Amendment to the National Interim Primary Drinking Water Regulations on Trihalomethanes - January, 1978.

The two exposure estimates, NAS (1978a) and the U.S. EPA (1978b) demonstrate that chloroform intake from ingesting water is likely to range from a modest to predominant percentage of total exposure with a simple minimum, mean, and maximum exposure scenario.

	% total exposure from water (U.S. EPA)	% total exposure from water (NAS)
Minimum Exposure	23%	6%
Mean Exposure	69%	67%
Maximum Exposure	61%	40%

Basis and Derivation of Criterion

Chloroform has several adverse effects on the human body. Safe levels of chloroform in water necessary to avoid some of these effects would be difficult to establish because adequate studies have not been conducted. The most serious effect to consider is the cancer-causing potential of the chemical. Current knowledge leads to the conclusion that carcinogenesis is a non-threshold, nonreversible process. The non-threshold concept implies that many tumors will be produced at high doses, but any dose, no matter how small, will have the probability of causing cancer. Even small carcinogenic risks have a serious impact on society when the exposed population is large, because it is likely that some cancers will be caused by chloroform. The nonreversible concept implies that once the tumor growth process has started, growth will continue and may metastasize and involve other organs until death ensues.

Chloroform has been shown to induce cancer in two species of experimental animals. This conclusion is neither confirmed nor denied by the results of numerous epidemiology studies now available although from a public health point of view, a suspicion of a qualitative weight of evidence for confirmation probably exists.

The available information on total human exposure to chloroform from air, water and food sources suggests that drinking water contributes from 6 percent to 69 percent of the total exposure. Considering that chloroform levels in drinking water are enhanced by water treatment processes on the one hand and that chloroform levels in waste discharges may be similarly enhanced by waste treatment processes, it is difficult to utilize the total exposure information in formulating an ambient water quality criterion, except to say that exposure through water is likely to be more significant than other exposure routes.

It is therefore proposed that the total risk for carcinogenic response be allocated to the ambient water exposure conditions of ingesting 2 liters/day of water and consuming 18.7 grams of potentially contaminated fish products.

Under the Consent Decree in NRDC vs. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." Chloroform is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of chloroform

in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and States in the possible future development of water quality regulations, the concentrations of chloroform corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6} or 10^{-7} as shown in the table below.

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1)			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish. (2)	0	0.021 µg/l	0.21 µg/l	2.1 µg/l
Consumption of fish and shellfish only.	0	0.175 µg/l	1.75 µg/l	17.5 µg/l

(1) Calculated by applying a modified "one-hit" extrapolation model described in the Methodology Document to the animal bioassay data presented in Appendix I and in Table 9. Since the extrapolation model is linear at low doses, the

additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1000, and so forth.

(2) Approximately 12 percent of the chloroform exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 14 fold. The remaining 88 percent of chloroform exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of chloroform, (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding chloroform concentrations and, (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding chloroform concentrations. Although total exposure information for chloroform is discussed and an estimate of the contributions from other sources of exposure can be made, this data will not be factored into ambient water quality criteria formulation until additional analysis can be made. The criteria presented, therefore, assume an incremental risk from ambient water exposure only.

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Appendix I

Derivation of Criterion for Chloroform

The NCI (1976) bioassay with female mice given a time-weighted average dose of 238 mg/kg of chloroform by stomach tube for 5 times per week for 78 weeks is used for the water quality criterion. The treatment induced hepatocellular carcinomas in 36 of 45 animals examined, whereas the pooled control group had one animal with hepatocellular carcinoma out of 80 animals examined. Assuming a fish bioaccumulation factor of 14, the parameters of the extrapolation model are:

$n_t = 36$

NT = 45

nc = 1

NC = 80

Le = 92 weeks

le = 78 weeks

d = 238 x 5/7 = 170 mg/kg/day

w = 0.030 kg

L = 92 weeks

R = 14.

F = .0187 kg

The result is that the water concentration should be less than 2.1 µg/l in order to keep the individual lifetime risk below 10^{-5}.